II. REMARKS

Formal Matters

Claims 2-8 and 11-15 are pending after entry of the amendments set forth herein.

Claims 1-15 were examined. Claims 1-7 and 9-12 were rejected. Claims 8 and 13-15 were withdrawn from consideration.

Claims 2-7 are amended. The amendments to the claims were made solely in the interest of expediting prosecution, and are not to be construed as an acquiescence to any objection or rejection of any claim. Support for the amendments to claim 2 is found in the claims as originally filed, and throughout the specification, in particular at the following exemplary locations: claim 2: page 6, lines 24-25. The amendments to claims 3-7 were made merely to amend the claim dependency. Accordingly, no new matter is added by these amendments.

Please replace claims 2-7 with the clean version provided above.

Claims 1, 9 and 10 are canceled without prejudice to renewal, without intent to acquiesce to any rejection, and without intent to surrender any subject matter encompassed by the canceled claims. Applicants expressly reserve the right to pursue any canceled subject matter in one or more continuation and/or divisional applications.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached is captioned "**VERSION WITH MARKINGS TO SHOW CHANGES MADE.**"

Applicants respectfully request reconsideration of the application in view of the remarks made herein.

Priority claim

The Office Action stated that the application lacks the necessary reference to the prior application. Applicants respectfully request entry of the amendment to the specification, as shown above.

Obviousness-type double patenting

Claims 1-7 and 9-12 were rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1-6, 8, 12, and 15-18 of U.S. Patent No. 5,998,209.

Without conceding as to the correctness of this rejection, a Terminal Disclaimer over U.S. Patent No. 5,998,209 is filed herewith.

Rejection under 35 U.S.C.§112, first paragraph

Claims 1-7 and 9-10 were rejected under 35 U.S.C.§112, first paragraph, as allegedly lacking enablement.

The Office Action stated that: (1) the specification is enabling for making a mammalian cells having a deletion of about 55 kb in a target locus; (2) the specification is does not reasonably provide enablement for making a deletion in the entire range of 15 kb to 3000 kb; (3) the state of the prior art was that a deletion of up to 19.2 kb was made in ES cells at the hprt locus, occurring at the same frequency as smaller deletions; and (4) it would require undue experimentation to practice the full scope of the claims. Applicants respectfully traverse the rejection.

The specification provides ample guidance for one of skill in the art to practice the invention without undue experimentation.

The instant specification provides ample guidance for those skilled in the art to practice the invention as claimed. The specification describes how to make a replacement targeting construct that includes a selectable marker and two regions of sequences that are homologous to the 5' and 3' flanking sequences of the targeted locus; how to introduce such a construct into a host cell; and how to select cells containing a deletion. Specification, page 6, lines 9-30; and page 8, lines 6-20. The specification provides a working example of the method. Specification, Example 1. The Example describes generation of a 55 kb deletion in a locus. Those skilled in the art, using the instant specification as guidance, could have readily made deletions of sizes other than 55 kb.

Ramirez-Solis does not support a conclusion of lack of enablement.

The Office Action stated that Zhang et al. ((1995) *Mol. Cell. Biol.* 14:2404-2410) shows deletions of up to 19.2 kb, and that Zhang stated that a wide spectrum of genomic deletions can be made. The Office Action further stated that Ramirez-Solis et al. ((1995) *Nature* 378:720-724), which published a year and a half later after Zhang, teaches that small deletions (20 kb) have been generated, but that larger deletions have not been possible. However, upon careful reading of Ramirez-Solis, one finds that Ramirez-Solis states, "Small deletions (20 kb) have been generated in embryonic stem (ES) cells by conventional gene targeting, but the constructions of larger deletions, inversions or duplications has not

been possible." As a basis for this statement, Ramirez-Solis cites Zhang et al. **Ramirez-Solis did not have access to the instant specification, which was not publicly available on December 14, 1995, when Ramirez-Solis was published.** Ramirez-Solis did not state that it is not possible to generate larger deletions using the method described in the instant specification, as Ramirez-Solis did not have access to the instant specification. Thus, Ramirez-Solis could not have commented on enablement of the instant invention as claimed.

Others have used the same technique to generate deletions of 100-200 kb.

The fact that those skilled in the art could generate deletions in the 50 to 3000 kb size range, using the method as claimed, and without undue experimentation, is demonstrated by the fact that others have published results showing that such deletions have been generated using the claimed methods. For example, Kimber et al. ((1999) *Human Molecular Genetics* 8:2229-2237; a copy of which is provided herewith as Exhibit 1) states that replacement-type targeting was used to produce 100-200 kB deletions. Kimber et al., page 2235, column 1, first paragraph under Materials and Methods. Kimber et al. used a targeting construct that included sequences from the 5' and 3' flanking regions of the targeted locus, flanking a sequence encoding neomycin resistance. Kimber et al., page 2231, Figure 1B.

Kimber et al., using the claimed method, generated deletions of approximately 150 kb. Accordingly, those skilled in the art, given the guidance provided in the instant specification, could readily generate deletions in the recited size range.

Applicants submit that the rejection of claims 1-7, 9, and 10 under 35 U.S.C. §112, first paragraph, has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

Rejection under 35 U.S.C.§112, second paragraph

Claims 1-7 and 9-12 were rejected under 35 U.S.C.§112, second paragraph, as allegedly indefinite.

Claim 1

The Office Action stated that claim 1 fails to recite positive process steps which clearly relate to the preamble, and suggested adding a correlation step. Claim 1 is canceled without prejudice to renewal, thereby rendering the rejection of this claim moot.

Claims 3-6

The Office Action stated that there is no antecedent basis for "said target locus."

Claim 2, from which claim 3-6 as amended depend, is amended to provide antecedent basis for "said target locus."

Claims 4 and 5

The Office Action stated that the terms "the MHC class I locus and "the MHC class II locus" render claims 4 and 5 vague and indefinite because MHC genes are found in several loci.

Claims 4 and 5 are amended to recite "an MHC class I locus" and "an MHC class II locus," respectively, thereby adequately addressing this rejection.

Applicants submit that the rejection of claims 1-7 and 9-12 under 35 U.S.C.§112, second paragraph, has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

Rejection under 102(b)

Claims 1-3, 7, and 9-10 were rejected under 35 U.S.C.§102(b) as allegedly anticipated by Zhang et al. ((1994) *Mol. Cell. Biol.* 14:2404-2410; hereinafter "Zhang").

The Office Action stated that Zhang teaches a method of targeting genomic deletions by homologous recombination of vectors that contain the same 5' vector arm, and 3' vector arms homologous to different positions in the gene. Claim 2 is re-written to include the limitations of claim 1, and to recite that the deletion is in a range of from about 50 kb to about 3000 kb. Zhang does not disclose a method for obtaining a mammalian cell comprising a genomic deletion in a range of from about 50 kb to about 3000 kb. According, Zhang cannot anticipate claims 2, 3, and 7. Claims 1, 9 and 10 are canceled without prejudice to renewal, thereby rendering this rejection of claims 9 and 10 moot.

Applicants submit that the rejection of claims 1-3, 7, and 9-10 under 35 U.S.C. §102(b) has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

Rejection under 35 U.S.C.§103

Claims 1-5, 7, and 9-10 were rejected under 35 U.S.C.§103 as allegedly unpatentable over Zhang in view of Kucherlapati et al. (U.S. Patent No. 5,413,923).

The Office Action stated that: (1) Zhang teaches a method of targeting genomic deletions by homologous recombination of vectors that contain the same 5' vector arm, and 3' vector arms that are homologous to different positions in the gene; (2) Zhang does not specifically teach deletion of a target locus which is the MHC class I or class II locus; (3) Kucherlapati teaches a method of inactivating MHC class I genes by homologous recombination between endogenous wild-type genes and a vector containing the MHC class I gene and flanking sequences using ES cells. The Office Action concluded that it would have been obvious to use the method of making large deletions up to about 19.2 kb, as taught by Zhang, in making deletions in any other genetic locus, such as MHC class I or II, as taught by Kucherlapati. Applicants respectfully traverse the rejection.

As noted above, claim 2 is re-written to recite the limitations of claim 1, and to recite that the deletion is in a range of from about 50 kb to about 3000 kb. Claims 1, 9 and 10 are canceled without prejudice to renewal, thereby rendering the rejection of these claims moot.

As discussed above, Zhang does not disclose a method for obtaining a mammalian cell comprising a genomic deletion in a range of from about 50 kb to about 3000 kb. Kucherlapati does not teach a method for obtaining a mammalian cell comprising a genomic deletion. Thus, Kucherlapati cannot make up for the deficiencies of Zhang as a primary reference.

Accordingly, Zhang, alone or in combination with Kucherlapati, cannot render instant claims 1-5 and 7 obvious.

Applicants submit that the rejection of claims 1-5, 7, and 9-10 under 35 U.S.C. §103 has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

III. CONCLUSION

Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number ABGX001CON3.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: March 7, 2002

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

Please insert the following text on page 1, after the title:

CROSS REFERENCE

This application is a continuation of U.S. Patent Application Serial No. 09/348,747, filed July 6, 1999, abandoned, which is a continuation of U.S. Patent Application Serial No. 08/808,139, filed February 28, 1997, now U.S. Patent No. 5,998,209, which is a continuation of U.S. Patent Application Serial No. 08/426,555, filed April 21, 1995, abandoned, each of which is incorporated by reference herein in their entirety.

Please enter the amendments to claims 2-7, as shown below.

2. (Amended) [The method of claim1 which further] A method for obtaining a mammalian cell comprising a genomic deletion in a range of from about 50 kb to about 3000 kb, which method comprises the steps of:

a) modifying the genome of mammalian cells comprising a wild-type target locus by introducing a construct comprising two regions of sequences that are homologous to the 5' and 3' flanking sequences of said wild-type target locus;

b) [a)] identifying cells containing said deletion by selecting cells containing a selectable marker present in said construct; and

c) [b)] recovering [cells containing] a mammalian cell comprising said deletion.

3. (Amended) The method of claim [1] 2 wherein said target locus is an [the] HPRT locus.

4. (Amended) The method of claim [1] 2 wherein said target locus is an [the] MHC Class I locus.

5. (Amended) The method of claim [1] 2 wherein said target locus is an [the] MHC Class II locus.

6. (Amended) The method of claim [1] 2 wherein said target locus is an [the] immunoglobulin locus.

7. (Amended) The method of claim [1] 2 wherein said mammalian cell is selected from the group consisting of the islets of Langerhans, adrenal medulla cells, osteoblasts, osteoclasts, epithelial cells, endothelial cells, B lymphocytes, T lymphocytes, neurons, glial cells, ganglion cells, retinal cells, keratinocytes, embryonic stem (ES) cells, liver cells, bone marrow cells, and muscle cells.